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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/601,324	06/20/2003	Ciaran N. Cronin	SYR-EPHA2-5001-C1	4969
32793 7590 06/15/2007 TAKEDA SAN DIEGO, INC. 10410 SCIENCE CENTER DRIVE SAN DIEGO, CA 92121			EXAMINER NOAKES, SUZANNE MARIE	
			ART UNIT 1656	PAPER NUMBER
			MAIL DATE 06/15/2007	DELIVERY MODE PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/601,324

Applicant(s)

CRONIN ET AL.

Examiner

Suzanne M. Noakes, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 March 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1,2,4,9,10,12,15,17,26,27 and 30-38 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 17,34 and 37 is/are allowed.
- 6) ☒ Claim(s) 1,2,4,9,10,12,15,26,27,30-33,35 and 36 is/are rejected.
- 7) ☒ Claim(s) 38 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- ☒ Notice of References Cited (PTO-892)
- ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- ☐ Notice of Informal Patent Application
- ☒ Other: See Continuation Sheet.

Continuation of Attachment(s) 6). Other: Appendix A - Proposed Ex. Amendment.

DETAILED ACTION

Status of the Application

1. Amendments to the claims filed 29 March 2007 are acknowledged. Applicants have cancelled claims 3, 5-8, 11, 13, 14, 16, 18-25 and 29 and added new claims 34-38. Claims 1, 2, 4, 9, 10, 12, 15, 17, 26, 27 and 30-38 are pending and under examination.

Withdrawal of Objections/Rejections

2. The rejection of claims 4 and 12 under 35 U.S.C. 112 2nd paragraph, recited in Section 12 of the previous Office action, is hereby withdrawn in view of Applicants amendments to the claims.

3. The rejection of claim 17 under 35 U.S.C. 112 1st paragraph, written description and enablement, as recited in Sections 13-15 in the previous Office action, is hereby withdrawn. Said withdrawal is necessitated by Applicants amendments to the claim which excludes the interpretation that said claim encompasses protein crystals.

Maintained Objections/Rejection

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Written Description:

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5. Claims 1, 2, 4, 9, 10, 12, 15, 26, 27, 30-33 and new claims 35 and 36 (said new claims, are commensurate in scope with the rejected claims) are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The details of the rejection is recited in the previous Office action in Section 10 and in Section 17 of the Office action from 10 April 2006.

Scope of Enablement:

6. Claims 1, 2, 4, 9, 10, 12, 15, 26, 27, 30-33 and new claims 35 and 36 (said new claims, are commensurate in scope with the rejected claims) are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement. The details of the rejection are recited in Section 11 of the previous Office action and Section 18 of the Office action from 10 April 2006.

Maintained Objections/Rejection – Necessitated by Amendment

Claim Objections

7. Claims 2, 32, 35, 36 and 38 objected to because of the following informalities.
- A. Claim 2 recites “dimmer” instead of ‘dimer’.
 - B. Claim 32 should recite “A method...”.

- C. Claims 35 and 36 recites "wherein the protein consists of 596-900 of SEQ ID No: 1". However, said claims should recite 'wherein the protein consists of residues 596-900 of SEQ ID No: 1.'
- D. Claim 38 should recite 'consisting' rather than "consists".

Appropriate correction is required.

New Rejections/Objections

Claim Rejections - 35 USC § 112 – 2nd paragraph

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 9, 31 and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 31 recites the limitation "The method of claim 26, further comprising measuring an activity of the protein when contacted with the on or more entities." There is insufficient antecedent basis for this limitation in the claim because claim 31 does not recite a "contacting" step. Furthermore, it is unclear to the Examiner if said claim should actually depend from claim 30, which does recite a contacting step.

B. Claims 9 and 36 are rejected as being indefinite because it is unclear whether or not the last clause of the claims: "forming a crystalline form of the protein in the crystallization volume" is thus required to have the same crystal

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space group and unit cell parameters recited earlier in the claims. It would be clearer if the last clause (e.g. forming a crystalline.....), came before the "wherein the protein crystal" clause.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 – 1st Paragraph

10. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 2, 10 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The specification states that there are two molecules in the *unit cell* (p. 25, paragraph 110), however, this does not necessarily mean that the molecule forms as a dimer. Furthermore, Figure 4 shows only a monomer, which appears to have two domains, but not a dimer. Furthermore, assuming that the protein did form a dimer, it is unclear why there are not two chains in .pdb files to reflect this as such. Instead, there are two independent .pdb files (figures 3A and 3B). Furthermore, no where else in the specification is any support found for the protein forming a dimer. Thus, this is deemed as a **New Matter** rejection.

Response to Arguments

12. Applicant's arguments filed 29 March 2007, and the accompanying amendments to the claims, have been fully considered but they are not persuasive.

Applicants arguments regarding the rejection of claims 1, 2, 4, 9, 10, 12, 15, 26, 27, 30-33 and new claims 35 and 36 is limited to the statement: "With regards to claims 1 and 9 (and claims dependent therefrom), the claims have been amended to recite the space group and unit cell dimensions, and as such, Applicants believe the rejections under 112, first paragraph for lacking written description and enablement should be withdrawn." (see Remarks, p. 5, 2nd to last paragraph). It should be noted, that new claims, 35 and 36 both also recite sequence number, unit cell parameters and space group, although, claims 35 and 36 differ from 1 and 9 by the protein sequence which is crystallized (SEQ ID No: 3 vs. SEQ ID No: 1, for claims 1/9 and claim 35/36, respectively).

The examiner has maintained both the written description and enablement rejections for the instant claims 1, 4, 9, 10, 12, 15, 26, 27, 30-33 because, while it is acknowledged that said claims do now possess a definite polypeptide sequence, space group and unit cell parameters, this insufficient given the information provided in the specification. Specifically, the crystals formed in the specification are co-crystals of SEQ ID No: 3 complexed to the ligand AMP-PNP. The crystals were obtained by forming the protein-AMP-PNP complex, *prior* to setting up the crystallization trials and thus most likely play a definitive role in forming the crystals. No apo-crystals were ever described. The prior art teaches that the use of ligands can completely change the

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crystallization parameters as compared to an apo-form of the same protein and that essentially one skilled in the art must begin anew to find different and alternative crystallization conditions (assuming an apo-crystal existed previously). McPherson (Eur. J. Biochem, 1990, 189 :1-23) states the following:

Substrates, coenzymes and inhibitors often serve to fix an enzyme in a more compact and stable form. Thus a greater degree of structural homogeneity may be imparted to a population of macromolecules and a reduced level of dynamic behavior achieved by complexing the protein a natural ligand before attempting its crystallization.

In some cases an apoprotein and its ligand complexes may be significantly different in their physical behavior and can, in terms of crystallization, be treated as almost entirely separate problems. This may permit a second or third opportunity for growing crystals if the native apoprotein appears refractile. Thus, it is worthwhile, when determining or searching for crystallization conditions, to explore complexes of the macromolecule with substrates coenzymes, analogues and inhibitors very early. In many ways, such complexes are inherently more interesting in a biochemical sense than the apoprotein when the structure is ultimately determined. (see p. 15, 1st column, 1st and 2nd full paragraphs).

Finally, it should be noted that the use of inhibitors or other ligands may sometimes be invoked to obtain a crystal form different from that grown from the native protein. When crystals of apoprotein are poorly suited for analysis, this may provide an alternative approach. (see p. 15, 1st column, 4th full paragraph).

Also, Dale et al. (J. Structural Biol., 2003, 142:88-97) teach methods to improve the chances that a protein will crystallize by modifying said protein of interest by co-crystallizing said protein with a ligand. It is specifically noted: "A protein may be modified in a number of ways to improve the chances of obtaining crystals. Many proteins that have not crystallized in their native state could be readily crystallized as complexes. Complex formation and subsequent co-crystallization screens can be performed with cofactors, inhibitors or even antibody fragments (citations omitted). The

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conformational changes induced upon such ligand binding may be favorable to the crystallization process by exposing new crystal contacts by stabilizing the protein." (see p. 89, 2nd column, 1st full paragraph).

Thus, considering what is taught in the prior art, co-crystallization with ligands, such as what Applicants did to obtain the only species of crystal in the specification, provides the proteins of interest with more favorable contacts and more homogeneous mixtures of proteins which may be favorable to successful crystallization. Furthermore, McPherson makes it clear that when crystallizing a native apo-protein and a complex of the same protein with a ligand often times results in completely independent and separate parameters and problems in the crystallization of any given protein.

McPherson outlines 25 different parameters which do or could affect crystallization (see Table 2, p. 13). It is stated (p. 13, 2nd column, *Factors influencing protein crystal growth*):

Table 2 lists physical, chemical and biological variables that may influence to a greater or lesser extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids. There are even cases where the identical protein prepared by difference procedures or at different times may show significant variations. In addition, each factor may differ considerably in importance for individual proteins.

It is noted that one of the factors is ligands. Thus, it is not enough to have the crystallization of a similar protein, an apo-protein or a "native" protein, rather what is required is the exact conditions of each and every protein crystal to be described in the specification in order to avoid undue experimentation. Furthermore, Applicants have

not described the given apo-protein in the specification and have not provided evidence of possession of this type of crystal. The single species which is representative, SEQ ID No: 3 complexed to AMP-PNP that forms in space group $P3_221$ with unit cell parameters of $\pm 5\%$ of $a=72.12\text{\AA}$, $b=72.12\text{\AA}$ and $c=241.62\text{\AA}$ is not representative of all species of proteins that form within said space group with the given unit cell parameters considering the unpredictability in the art. It is noted that for inventions in emerging and unpredictable technologies, or for inventions characterized by factors not reasonably predictable which are known to one of ordinary skill in the art, more evidence is required to show possession. For example, disclosure of only a method of making the invention and the function may not be sufficient to support a product claim other than a product-by-process claim. See, e.g., *Fiers v. Revel*, 984 F.2d at 1169, 25 USPQ2d at 1605; *Amgen*, 927 F.2d at 1206, 18 USPQ2d at 1021.

With regards to new claims 35 and 36, these claims suffer from the arguments recited above because of the lack of recitation of the required ligand in the claim. However, the claims also lack enablement and written description because no crystals were ever formed with just amino acids 596-900 of SEQ ID No: 1. Rather SEQ ID No: 3 was used, wherein said protein differs from amino acids 596-900 of SEQ ID No: 1 by an additional 28 amino acids at the N-terminus, wherein SEQ ID No: 3 has a cleavable (rTev) N-terminal 6x-histidine tag (see SEQ ID No: 3 in sequence listing). The specification specifically states: "It is noted that the polyhistidine tags may optionally be removed by treatment with rTEV protease (Invitrogen). However, in this instance, the polyhistidine tag was not removed." (see specification, p. 48, paragraph

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00200). The unpredictability of whether or not a protein crystallized with a His-tag, will also crystallize without a His-Tag in the same space group and with the same unit cell parameters is unpredictable at best, or *if* said protein will even crystallize in the first place. A skilled artisan has no way of knowing if the removal of the his-tag will or will not affect the proteins ability to crystallize, despite the fact that it is flexible or might not be involved in crystal contacts. This can be seen by reviewing a 2001 summary collection of correspondence between artisans skilled in the art of protein crystallography on the CCP4 Bulletin Board addressing the successes, or not, of protein crystallization with/without His-Tags, wherein 5 - 6 skilled artisans weighed in on the matter of His-Tags and protein crystallization. As one can see, there is no straight answer, what works for one person, does not for another. Some skilled artisans assert that His-tags will inhibit crystallization, others, assert cleaving the His-tag helps, while others state the their protein crystallizes with the His-tag cut off/cleaved, but does not crystallize when the His-tag is left on (see #3). The ambiguity in the art is hit or miss at best and this is specifically echoed in the summary statement made by Bernhard Rupp (#4):

"[Anekdotical] case examples exist either way, we had a 68 residue tag on a (large) protease and it diffracted to 1.8 Å, others report even the vicinity of his-tag plasmid containing vial in the same room as crystals jinxes theirs. All of the above translates into ***we have no clue***, because we seldom hear about negatives, which we would need to establish proper statistics. So maybe after unbiased Structural genomics data bases have been filled, we may be able to give a likelihood of reduced/increased success of His- vs Non-tagged constructs."

It should be noted that Bernhard Rupp is the Head of the Macromolecular Crystallography and Structural Genomics Group, UC-LLNL (Lawrence Livermore National Laboratory) and has published over 120 peer reviewed journal articles dealing with protein crystallography, four text books on protein crystallography, 31 protein crystal structures submitted to the Protein Data Bank and 16 US patents concerning protein crystallography. Thus it is deemed that Dr. Rupp is one skilled in the art of protein crystallography.

Conclusion

13. Claims 17, 34 and 37 are allowed. Claim 38 is objected to for minor informalities but will be in condition for allowance once said informalities have been addressed. Claims 1, 2, 4, 9, 10, 12, 15, 26, 27, 30-33, 35 and 36 are rejected for the reasons noted above.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Suzanne M. Noakes, Ph.D. whose telephone number is 571-272-2924. The examiner can normally be reached on Monday to Friday, 7.00am to 3.30pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SMN

31 May 2007

Surge M. Noakes
Examiner AU 1656

Appendix A



UNITED STATES PATENT AND TRADEMARK OFFICE

Facsimile Transmission

To:	Name:	Robin Silva
	Company:	
	Fax Number:	914154421001
	Voice Phone:	
From:	Name:	Suzanne M. Noakes, Ph.D.
	Voice Phone:	571-272-2924

37 C.F.R. 1.6 sets forth the types of correspondence that can be communicated to the Patent and Trademark Office via facsimile transmissions. Applicants are advised to use the certificate of facsimile transmission procedures when submitting a reply to a non-final or final Office action by facsimile (37 CFR 1.8(a)).

Fax Notes:

Ms. Silva,

Please consider the proposed Ex. Amendment for 10601324. No support in spec for xtals without His-tag I am afraid....also ligand AMP-PNP needs to be in independent claim as proposed here. Please give me a call with any questions.

Thanks as always,
Suzanne Noakes
571-272-2924

Date and time of transmission: Thursday, April 05, 2007 1:11:10 PM
Number of pages including this cover sheet: 03

PROPOSED EXAMINER'S AMENDMENT

DRAFT ONLY

1. An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it **MUST** be submitted no later than the payment of the issue fee.

Authorization for this examiner's amendment was given in a telephone interview with *** on ***.

The application has been amended as follows:

In the claims:

- Rewrite claim 1 as follows: A composition comprising a protein in crystalline form wherein the protein consists of SEQ ID No: 3, wherein said protein forms a complex with AMP-PNP, and wherein the protein crystal has a crystal lattice in a P₃₂21 space group and unit cell dimensions, +/- 5% of a=72.12 Å, b= 72.12 Å, and c=241.62 Å.
- Rewrite claim 9 as follows: A method comprising: forming a crystallization volume comprising a precipitant solution and a protein consists of SEQ ID No: 3, wherein said protein forms a complex with AMP-PNP, wherein the protein crystal has a crystal lattice in a P₃₂21 space group and unit cell dimensions, +/- 5% of a=72.12 Å, b= 72.12 Å, and c=241.62 Å; and forming a crystalline form of the protein in the crystallization volume.
- In claim 2, delete - - - dimmer - - - and substitute therefor - - - dimer - - -.

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- In claim 32, insert - - - A - - - as the first word of the claim.
- In claim 38, delete - - - consists - - - and substitute therefor - - - consisting - - -.
- Cancel claims 35 and 36.

ALLOWED claims would be 1, 2, 4, 9, 10, 12, 15, 17, 26, 27, 30-34, 37 and 38.

DRAFT ONLY